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Molecular basis of potassium channels in pancreatic duct epithelial cells

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Abbreviations: AKAP, A-kinase anchoring protein; BK, voltage – and Ca^{2+}-dependent maxi-K^+; BxPC3, human pancreas adenocarcinoma cell line; Capan-1, human pancreas adenocarcinoma cell line; CFPAC-1, human cystic fibrosis pancreatic adenocarcinoma cell line; CFTR, cystic fibrosis transmembrane conductance regulator; DC-EBIO, 5,6-dichloro-1-ethyl-1,3-dihydro-2*H*-benzimidazole-2-one; DHS-I, dehydrosoyasaponin I; DIDS, 4,4'-diisothiocyanatostilbene-2,2'-disulfonic acid; E-4031, *N*-[4-[1-[2-(6-methylpyridin-2-yl)ethyl]piperidine-4-carbonyl]phenyl] methanesulfonamide; EAG, ether-à-go-go gene; 1-EBIO, 1-ethyl-2-benzimidazolinone; HERG, human ether-à-go-go related gene; HPAF, human pancreatic ductal adenocarcinoma cell line; ICA-105574, 3-nitro-*N*-(4-phenoxyphenyl) benzamide; IK, intermediate-conductance Ca^{2+}-activated K^+; I_{sc}, short-circuit current; K_{2P}, two-pore domain K^+ channels; K_{ir}, inward rectifier potassium channel; L-364,373, (3-*R*)-1,3-dihydro-5-(2-fluorophenyl)-3-(1*H*-indol-3-ylmethyl)-1-methyl-2*H*-1,4-benzodiazepin-2-one; LY97241, *N*-ethyl-*N*-[4-(4-nitrophenyl)butyl]heptan-1-amine; NS11021, 1-(3,5-bis-trifluoromethyl-phenyl)-3-[4-bromo-2-(1*H*-tetrazol-5-yl)-phenyl]-thiourea; NS1608, *N*-(3-(trifluoromethyl)phenyl)-*N'*-(2-hydroxy-5-chlorophenyl)urea; PD-118057, [2-(4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino)-benzoic acid; PKA, cAMP-dependent protein kinase; PKC, protein kinase C; PMA, phorbol 12-myristate 13-acetate; Ro-20-1724, 4-(3-butoxy-4-methoxybenzyl)-2-imidazolidinone; Slack, sequence like a calcium-activated K^+ channel; Slick, sequence like an intermediate conductance K^+ channel; TALK, TWIK-related alkaline pH-activated K^+ channel; TASK, TWIK–related acid-sensitive K^+ channel; TRAM-34, 1-[(2-chlorophenyl)diphenylmethyl]-1*H*-pyrazole; TWIK, tandem of P-domains in a weak inward rectifying K^+ channel; $V_{1/2}$, half-maximal voltage; XE991, 10,10-bis(4-pyridinylmethyl)-9(10*H*)-anthracenone

Potassium channels regulate excitability, epithelial ion transport, proliferation, and apoptosis. In pancreatic ducts, K^+ channels hyperpolarize the membrane potential and provide the driving force for anion secretion. This review focuses on the molecular candidates of functional K^+ channels in pancreatic duct cells, including *KCNN4* ($K_{Ca}3.1$), *KCNMA1* ($K_{Ca}1.1$), *KCNQ1* ($K_v7.1$), *KCNH2* ($K_v11.1$), *KCNH5* ($K_v10.2$), *KCNT1* ($K_{Ca}4.1$), *KCNT2* ($K_{Ca}4.2$), and *KCNK5* ($K_{2P}5.1$). We will give an overview of K^+ channels with respect to their electrophysiological and pharmacological characteristics and regulation, which we know from other cell types, preferably in epithelia, and, where known, their identification and functions in pancreatic ducts and in adenocarcinoma cells. We conclude by pointing out some outstanding questions and future directions in pancreatic K^+ channel research with respect to the physiology of secretion and pancreatic pathologies, including pancreatitis, cystic fibrosis, and cancer, in which the dysregulation or altered expression of K^+ channels may be of importance.

Introduction

Potassium channels (K^+ channels) are very important membrane proteins present in every cell. They determine the cell membrane potential and thereby regulate the excitability of neurons and myocytes and transport of ions and water in epithelia, such as the pancreas and salivary glands. Duct epithelial cells in the pancreas secrete a HCO_3^--rich pancreatic juice that neutralizes acid chyme in the duodenum. Secretin, acetylcholine, and ATP stimulate fluid secretion via signal transduction involving cAMP and Ca^{2+} signaling pathways. The generally accepted model for HCO_3^- transport involves Cl^-–HCO_3^- exchangers (SLC26A3 and SLC26A6) that operate in parallel with cAMP-activated Cl^- channels (CFTR) or Ca^{2+}-activated Cl^- channels (most likely TMEM16A) on the luminal membrane and Na^+-coupled transporters such Na^+–K^+–Cl^- co-transporter (NKCC1), Na^+–HCO_3^- co-transporter (SLC4A4), and Na^+–H^+ exchanger (SLC9A1) and Na^+–K^+-pump on the basolateral membrane (**Fig. 1**).[1-3] In addition, H^+–K^+-pumps are expressed on the luminal and basolateral membranes of pancreatic ducts.[4] K^+ channels are clearly important for setting the resting membrane potential and providing the driving force for anion exit and fluid secretion in a stimulated epithelium.[1-3,5] K^+ channels may also provide the transport partners for H^+–K^+-pumps.[4] In addition, certain K^+ channels could play an important role in pancreatic pathology, such as cystic fibrosis, pancreatitis, and pancreatic adenocarcinoma. Perhaps surprisingly, there are not so many K^+ channels studies performed on pancreatic ducts.

Early electrophysiological studies using microelectrodes and patch-clamp methods indicated that pancreatic ducts expressed voltage- and Ca^{2+}-activated K^+-channels, consistent with maxi-K^+ channels (BK channels), intermediate-conductance Ca^{2+}-activated

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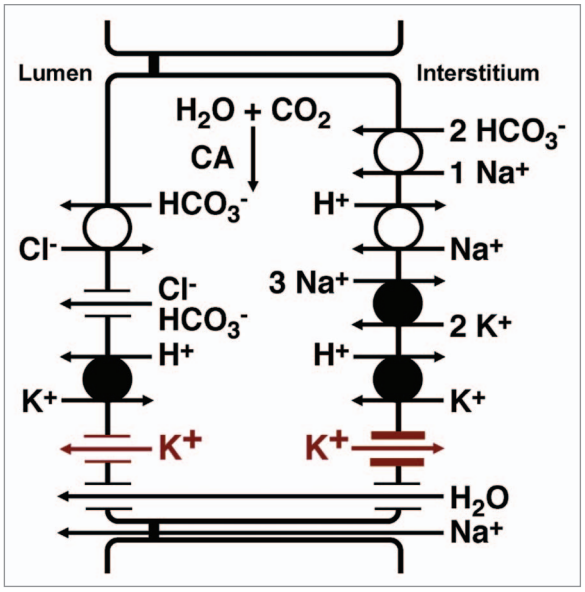

Figure 1. Model of ion transport in a pancreatic duct cell. Intracellular HCO_3^- is derived from CO_2 through the action of carbonic anhydrase (CA) and from HCO_3^- uptake via the Na^+–HCO_3^- cotransporter. H^+ is extruded at the basolateral membrane by the Na^+–H^+ exchanger and H^+–K^+ pump. HCO_3^- efflux across the luminal membrane is mediated by Cl^-–HCO_3^- exchangers and/or Cl^- channels, and the H^+–K^+ pump may provide a buffering/protection zone for the alkali-secreting epithelium. K^+ channels provide an exit pathway for K^+ and play a vital role in maintaining the membrane potential, which is a crucial component of the driving force for anion secretion.

K^+ channels (IK channels), and pH/HCO_3^- sensitive K^+ channels.[6-13] Recent studies focusing on molecular candidates have shown that pancreatic ducts express the following channels that could be candidates for above functional channels: $K_{Ca}1.1$ channels coded by the *KCNMA1* and *KCNMB1* genes (α – and β-subunits of the BK channel); the $K_{Ca}3.1$ protein coded by the *KCNN4* gene (IK channel); the *KCNK5* gene ($K_{2p}5.1$); and they also express: *KCNQ1* ($K_v7.1$, KVLQT1), *KCNH2* ($K_v11.1$, HERG), *KCNH5* ($K_v10.2$, EAG2), *KCNT1* ($K_{Ca}4.1$, Slack), and *KCNT2* ($K_{Ca}4.2$, Slick), the functions of which remain unclear in duct cells.[10,11,13]

It is not known whether many of these candidates are functional in pancreatic ducts or what is their localization and regulation. Therefore, their physiological and possibly pathophysiological functions have not to be confirmed. The aim of this review is to provide an overview of the above mentioned K^+ channels with respect to their electrophysiological and pharmacological characteristics and functions, as we know from other cell types, preferably in epithelia, and, where known, their identification and functions in pancreatic ducts is given (**Table 1**). We also address some outstanding questions and future directions in pancreatic K^+ channel research.

KCNN4 ($K_{Ca}3.1$, IK, SK4)

Tissue expression

KCNN4 coding for the $K_{Ca}3.1$ protein was cloned from the placenta and pancreas.[14,15] Functional expression of the *KCNN4* gene has been demonstrated in colonic crypts,[16] salivary acini,[17-19] and pancreatic ducts.[11,13] Immunoreactivity of the $K_{Ca}3.1$ protein has also been reported in the esophagus, stomach, small intestine, proximal colonic crypts, salivary glands, luminal membrane of lacrimal gland duct cells,[20-22] and intercalated and intralobular ducts of the pancreas.[13,23] Interestingly, $K_{Ca}3.1$ channel immunoreactivity was shown to be localized in both the basolateral and luminal membranes in pancreatic ducts and monolayer of Capan-1, a human pancreas adenocarcinoma cell line, though its expression appeared to be stronger in the luminal membrane. Consistent with this finding, the short-circuit current (I_{sc}) of the Capan-1 cell monolayer was enhanced by the $K_{Ca}3.1$ channel activator DC-EBIO in luminal or basolateral bathing solution.[13,24] $K_{Ca}3.1$ could potentially be an important candidate for luminal K^+ channels in pancreatic ducts. Importantly, equivalent-circuit analysis revealed that luminal K^+ conductance contributed to a minimum of 10% of the total K^+ conductance in pancreatic duct cells.[8] Moreover, stimulation of the rat pancreas with secretin caused a marked increase in K^+ concentrations in the pancreatic juice, which was equal to twice that in the plasma, indicating that K^+ was secreted.[25] K^+ efflux was also shown to be mediated via mucosal $K_{Ca}3.1$ channels in other epithelia, such as the distal colon, and provided, in part, the driving force for agonist-induced anion secretion.[26] Another example is salivary acini, in which both $K_{Ca}1.1$ and $K_{Ca}3.1$ were shown to be expressed on the apical membrane and contribute to optimal secretion.[27] Furthermore, H^+–K^+-pumps were reported to be expressed on the luminal membranes of pancreatic ducts[4] and their function, such as contributing to local epithelial protection, appeared to depend on the operation of K^+ channels.

Channel properties

Patch-clamp studies using *Xenopus* oocytes and mammalian expression systems established the basic electrophysiological and pharmacological properties of $K_{Ca}3.1$ channels.[15,28,29] Single-channel openings were observed at both positive and negative membrane potentials, and this gating showed no significant voltage dependency. The single-channel current–voltage relationship showed weak inward rectification with conductance of 30–54 pS in heterologous expression systems. Interestingly, intermediate-conductance K^+ channels exhibited a conductance of 80 pS in rat pancreatic duct cells.[13] One explanation for this discrepancy is that unidentified auxiliary proteins for $K_{Ca}3.1$ channels or additional *KCNN4* genes may exist in rodent cells. Regarding pharmacology, $K_{Ca}3.1$ currents were inhibited by charybdotoxin, clotrimazole, TRAM-34, and maurotoxin with K_i values of 2–28 nM, 25–150 nM, 20 nM, and 1 nM, respectively.[15,28-32] $K_{Ca}3.1$ currents were also activated by 1-EBIO and DC-EBIO with K_d values of 15–84 μM and 0.8 μM, respectively.[28,29,31,33]

Regulation

Regarding regulation, it is well established that $K_{Ca}3.1$ channels are activated by the Ca^{2+}/calmodulin signaling pathway. For example, heterologously expressed $K_{Ca}3.1$ channels were previously shown to be activated by submicromolar free Ca^{2+} concentrations with EC_{50} values of 0.1–0.3 μM.[14,15,29,31] There is also strong evidence to suggest that the Ca^{2+} sensitivity of $K_{Ca}3.1$ channels is mediated by calmodulin and calmodulin

Table 1. Molecular candidates of functional K^+ channels in pancreatic duct cells

Gene	Protein	Conductance (p)S)	Blockers (K_i)	Activators (K_d)	Regulation
KCNN4	$K_{Ca}3.1$	30–54[15,28,29]	charybdotoxin (2–28 nM)[15,28,29,31] clotrimazole (25–150 nM)[15,28-31] TRAM-34 (20 nM)[30] maurotoxin (1 nM)[32]	1-EBIO (15–84 μM)[28,29,31,33] DC-EBIO (0.8 μM)[33]	Ca^{2+} [14,15,29,31] calmodulin[18,29,34] PKA[19,42,43] extracellular UTP[11] cell swelling[47,48]
KCMA1	$K_{Ca}1.1$	100–270[50,56]	tetraethylammonium (0.14 mM)[50] charybdotoxin (1–31 nM)[57,58,62] iberiotoxin (1–9 nM)[58,61,62] paxilline (2–9 nM)[58-60]	NS1608 (2 μM)[60] NS11021 (0.4 μM)[63]	membrane potential[7,50,56,64] Ca^{2+} [7,50,56,64] PKA[7,56] extracellular UTP[11]
KCNQ1	$K_v7.1$	0.7–4[80,81]	chromanol 293B (10–41 μM)[68,82,86,87] azimilide (77 μM)[86] XE991 (0.8 μM)[88]	L-364,373[90]	membrane potential[78-81] cAMP[91] cytosolic pH[83]
KCNQ1/ KCNE1	$K_v7.1$/ minK	4.5–16[80,81]	chromanol 293B (3–10 μM)[70,82,86,87] azimilide (5.6 μM)[86] XE991 (11 μM)[88] Mefloquine (0.9 μM)[89]	DIDS[86] mefenamic acid[86]	membrane potential[78-81] cAMP[91,92] cytosolic pH[83]
KCNH2	$K_v11.1$	10–13[102-104]	E-4031 (7–1250 nM)[104,105,108-111] BeKm-1 (3–12 nM)[106-110] ergtoxin (4.5–17 nM)[107,109] LY97241 (2.2–19 nM)[111,112]	mallotoxin (0.5 μM)[114] PD-118057 (3.1 μM)[115] ICA-105574 (0.5 μM)[108]	membrane potential[116] PKA[119,120]
KCNH5	$K_v10.2$		LY97241 (1.5 μM)[113]		membrane potential[97] PKC[97]
KCNT1	$K_{Ca}4.1$	180[122]	bepridil (1 μM)[125] quinidine (90 μM)[125]	bithionol (0.8 μM)[125] niclosamide (2.9 μM)[126] loxapine (4.4 μM)[126] niflumic acid (2.7 mM)[127]	membrane potential[121,122] Ca^{2+} [121] Na^+ [122,123] Cl^- [123] PKC[130]
KCNT2	$K_{Ca}4.2$	140[122]	quinidine[122] isoflurane[128]	meclofenamic acid (80 μM)[127] flufenamic acid (1.1–1.4 mM)[127,129] niflumic acid (2.1 mM)[127,129]	membrane potential[122] Na^+ [122,130] Cl^- [122] intracellular ATP[122] PKC[130]
KCNK5	$K_{2P}5.1$	50–78[133,136,137]	quinine (22 μM)[133] clofilium (25 μM)[138] bupivacaine (26 μM)[139] ropivacaine (95 μM)[139]	halothane, isoflurane, chloroform[140]	extracellular pH[133,138,140,141] PKC[140] osmolality[138]

kinase.[18,29,34] In addition, ATP/UTP was shown to regulate $K_{Ca}3.1$ channels via purinergic receptors in pancreatic cell lines and rat pancreatic duct cells.[10,12,24,35] Both $P2Y_2$ and $P2Y_4$ receptors upregulated $K_{Ca}3.1$ activity in the *Xenopus* oocyte expression system.[11] Importantly, luminal ATP/UTP, most likely delivered by secreting acini,[36,37] was reported to stimulate ductal secretion.[24,35,38-41]

The physiological role of $K_{Ca}3.1$ channels in pancreatic secretion could be also investigated with respect to secretin, which acts predominantly via the cAMP/cAMP-dependent protein kinase (PKA) signaling pathway, however, until this becomes available, we need to resort to studies on other cell types. A membrane-associated PKA has been proposed to activate $K_{Ca}3.1$ channels

in human erythrocytes, the T84 human colonic crypt cell line, and rat submandibular acinar cells.[19,42,43] Interestingly, the PKA consensus phosphorylation site at serine 334 in $K_{Ca}3.1$ channels was not involved in PKA-dependent activation.[43] In contrast to these studies, heterologously expressed $K_{Ca}3.1$ channels were not affected by PKA activators and/or inhibitors,[29,44] or were inhibited by the catalytic subunit of PKA.[45] Given these contradictory results, it is tempting to speculate that $K_{Ca}3.1$ channels may be activated via the phosphorylation of a closely associated protein, the expression of which is tissue-specific. One candidate for this protein is A-kinase anchoring protein (AKAP), which is able to scaffold PKA and components of cAMP signaling pathways, including G protein-coupled receptors and ion channels.[46]

In addition to transepithelial transport, $K_{Ca}3.1$ channels were also shown to be stimulated by cell swelling, which triggered regulatory volume decreases.[47,48] Notably, *KCNN4* mRNA levels were upregulated in primary pancreatic tumors, and the growth of ductal adenocarcinoma cell lines in vitro was inhibited by blockers of $K_{Ca}3.1$ channels, which indicated that these were correlated with the proliferation of pancreatic cancer.[49]

KCNMA1 ($K_{Ca}1.1$, Slo1, α-subunit of BK) and KCNMB (β-subunits)

Tissue expression

The *KCNMA1* coding $K_{Ca}1.1$ (Slo1) protein was cloned from brain and skeletal muscle.[50] Functional expression of the *KCNMA1* gene has been demonstrated in the colon,[51] salivary acini,[17] pancreatic acini,[52] and pancreatic ducts.[11,53] The $K_{Ca}1.1$ protein is located in the luminal membrane of colonic epithelia,[51,54] salivary acini and ducts,[27,55] and pancreatic ducts.[53] It is noteworthy that there was no labeling of the basolateral membrane of guinea-pig pancreatic duct cells, although the first recordings of maxi-K^+ currents were made on the basolateral membrane of rat pancreatic ducts.[7] Venglovecz et al.[53] proposed that luminal $K_{Ca}1.1$ channels, which are activated by bile acids in the lumen, regulate HCO_3^- secretion in pancreatic ducts. Nevertheless, experiments on $K_{Ca}1.1$ regulation have also indicated that some channels may be confined to the basolateral membrane (see below). Luminal $K_{Ca}1.1$ channels in the distal colon were shown to be responsible for resting and stimulated Ca^{2+}-activated K^+ secretion.[51]

Channel properties

$K_{Ca}1.1$ channels have the largest single-channel conductance of all K^+ selective channels: 100–270 pS in symmetrical 150 mM KCl.[50,56] Maxi-K^+ currents in isolated rat pancreatic duct cells had a conductance of 170–180 pS.[7,13] Regarding pharmacology, the α-subunit of $K_{Ca}1.1$ was inhibited by tetraethylammonium, charybdotoxin, iberiotoxin, and paxilline with K_i values of 0.14 mM, 1–31 nM, 1–9 nM, and 2–9 nM, respectively.[50,57-62] The α-subunit of $K_{Ca}1.1$ was also activated by NS1608 and NS11021 with K_d values of 2 μM and 0.4 μM, respectively.[60,63] Interestingly, dehydrosoyasaponin I (DHS-I) activated the α-subunit of $K_{Ca}1.1$ only if co-expressed with the β1-subunit, an auxiliary protein for $K_{Ca}1.1$ channels.[57]

Regulation

Significant diversity has been reported in the functional characteristics of $K_{Ca}1.1$ channels. It is well established that $K_{Ca}1.1$ channels are activated by membrane depolarization alone, intracellular Ca^{2+} alone, or synergistically by depolarization and Ca^{2+}.[7,50,56,64] The single-channel open probability of $K_{Ca}1.1$ channels markedly increased when the cytoplasmic face of a patch membrane was exposed to 10 μM Ca^{2+} and voltage was changed over a range of −60 to +80 mV. Under these conditions, the half-maximal voltage ($V_{1/2}$) was +23 mV in 10 μM Ca^{2+};[50] however, these were unphysiological conditions for pancreatic ducts. Importantly, maxi-K^+ channels on pancreatic duct cells were activated by much lower Ca^{2+} concentrations. For example, maxi-K^+ channels exposed to 3 μM Ca^{2+} reached $V_{1/2}$ at −4 mV.[7] This difference indicated that the β-subunit exists in pancreatic duct cells. Maxi-K^+ channels on *Xenopus* oocytes that heterologously expressed both the α – and β1-subunits of $K_{Ca}1.1$ proteins were about 10-fold more sensitive to activation by voltage and Ca^{2+} concentration than channels composed of the α-subunit alone.[57] Indeed, *KCNMB1* coding the β1 subunit was detected in isolated pancreatic ducts.[11]

Interestingly, UTP was shown to inhibit $K_{Ca}1.1$ channels via the $P2Y_2$ receptor,[11] and appeared to lead to a decrease in secretion. The basolateral application of ATP/UTP inhibited K^+ conductance in rat duct cells and secretion in guinea-pig ducts and human duct cell monolayers.[35,39,40] These results collectively indicated that $P2Y_2$ receptors on the basolateral membrane appeared to downregulate secretion via $K_{Ca}1.1$ channels in the ductal system.

Regarding the cAMP/PKA signaling pathway, cAMP-dependent phosphorylation can also activate maxi-K^+ channels on pancreatic duct cells.[7] The functional response of $K_{Ca}1.1$ channels to PKA phosphorylation depends on the splice-variant of the α-subunit. For example, PKA was shown to activate the ZERO splice variant, whereas PKA inhibited the STREX variant. PKA activation of the ZERO variant requires a conserved C-terminal PKA site.[65] Indeed, the ZERO splice variant has been shown to conduct adrenaline-induced K^+ secretion in the distal colon.[66]

KCNQ1 ($K_v7.1$, KVLQT1) and KCNE1 (minK)

Tissue expression

The *KCNQ1* coding $K_v7.1$ protein was cloned from the heart.[67] Functional expression of the *KCNQ1* gene has also been demonstrated in the kidney, stomach, small intestine, colon,[68-71] pancreatic acini,[69,72,73] and pancreatic ducts.[13] Immunoreactivity of the $K_v7.1$ protein was reported in the parietal cells of the stomach, in the basolateral membrane of small intestinal and colonic crypt cells,[69,74,75] and in acinar and duct cells of the pancreas.[13,69] $K_v7.1$ resides in the tubulovesicular and canalicular membranes of gastric parietal cells together with H^+–K^+-pumps and participates in gastric acid secretion.[71,74,75] $K_v7.1$ was localized in the luminal membrane of pancreatic duct cells,[13] and may be involved in cell volume regulation during purinergic stimulation in epithelial transport,[76,77] and/or may potentially be associated with H^+–K^+-pumps expressed by pancreatic ducts.[4]

The K_v7.1 protein can assemble with the *KCNE* family of regulatory β-subunits to fulfill various physiological functions. For example, minK coded by the *KCNE1* gene has been shown to modify K_v7.1 activity by increasing unitary conductance, slowing activation, causing a right shift in the voltage dependence of activation, and modulating pharmacology.[78-82] It is worth noting that the acidification of cytosolic pH increased K_v7.1–minK, but decreased K_v7.1 currents, whereas alkalinization decreased K_v7.1–minK, but increased K_v7.1 currents.[83] Indeed, the whole pancreas expresses *KCNE1* and *KCNE2* genes.[84,85] The K_v7.1 current was shown to be strongly diminished and membrane targeting of the K_v7.1 protein was impaired in acinar cells in *KCNE1* knockout mice.[69] The expression and function of *KCNE* in duct cells has not yet been investigated.

Channel properties

K_v7.1 channels have very small conductance. Noise analysis revealed estimated single-channel conductances of 0.7–4 pS.[80,81] Small conductance K^+ channels had 1 pS and were inhibited by chromanol 293B, a K_v7.1 blocker, in the basolateral membrane of rat pancreatic acinar cells.[73] Chromanol 293B inhibited α-subunit of K_v7.1 with K_i values of 10–41 μM in *Xenopus* oocytes and mammalian expression systems.[68,82,86,87] Importantly, *KCNE* β-subunits increase the sensitivity of K_v7.1 to chromanol 293B. K_i values for K_v7.1/KCNE1, K_v7.1/KCNE2 and K_v7.1/KCNE3 were 3–10 μM, 0.4 μM, and 3–4 μM, respectively.[68,70,82,86,87] Voltage-gated K^+ currents in pancreatic acinar cells were shown to be inhibited by chromanol 293B with a K_i value of 3 μM.[72] This result supports voltage-gated K^+ channels being composed of K_v7.1 and *KCNE1* β-subunit in acinar cells. Azimilide inhibited K_v7.1 and K_v7.1/KCNE1 in the same manner as chromanol 293B with K_i values of 77 μM and 5.6 μM, respectively.[86] In contrast, XE991 inhibited K_v7.1 and K_v7.1/KCNE1 with K_i values of 0.8 μM and 11 μM, respectively.[88] Mefloquine inhibited K_v7.1/KCNE1 with a K_i value of 0.9 μM.[89] DIDS and mefenamic acid activated K_v7.1/KCNE1, but not K_v7.1.[86] On the other hand, L-364,373 activated K_v7.1, but did not affect K_v7.1/KCNE1.[90]

Regulation

Regarding regulation, voltage-gated K_v7.1 channels are known to be regulated by the cAMP signaling pathway.[91] In addition, AKAPs are required for cAMP regulation of recombinant K_v7.1 channels in mammalian cell lines.[92] Interestingly, a K^+ current was elicited by cAMP stimulation in CFTR-transfected, but not untransfected CFPAC-1 cells derived from a cystic fibrosis patient with deletion in Phe-508 in CFTR.[93] AKAPs also mediate PKA compartmentalization with CFTR;[94] therefore, these findings imply that functional CFTR regulates the K_v7.1 channel, presumably in the luminal membrane of pancreatic duct cells.

KCNH2 (K_v11.1, HERG) and *KCNH5* (K_v10.2, EAG2)

Tissue expression

The *KCNH2* coding K_v11.1 (HERG) protein was isolated from the hippocampal cDNA library.[95] Functional expression of the *KCNH2* gene has been demonstrated in colon carcinoma cells.[96] Immunoreactivity of the K_v11.1 protein was also reported in colon carcinoma cells[96] and the luminal membrane of pancreatic duct cells.[13] The *KCNH5* coding K_v10.2 (EAG2) protein was identified in the thalamus and was expressed in the brain, testes, skeletal muscle, heart, placenta, lung, liver, and at low levels in the kidney and whole pancreas.[97,98] Notably, K_v10.2 was shown to promote medulloblastoma tumor progression by regulating cell volume dynamics.[99] *KCNH2* and *KCNH5* are clearly expressed in rodent and human pancreatic duct cells.[13] However, the physiological or potentially pathophysiological role of K_v11.1 and K_v10.2 channels remains unclear. The related K_v10.1 (*KCNH1*) channel has been shown to be upregulated in several cancers including pancreatic cancer, based on studies of human pancreatic adenocarcinoma cell lines.[100,101]

Channel properties

K_v11.1 channels have small conductance of 10–13 pS.[102-104] Regarding pharmacology, K_v11.1 was inhibited by E-4031, BeKm-1, and ergtoxin with K_i values of 7–1250 nM, 3–12 nM, and 4.5–17 nM, respectively.[104-111] K_v11.1 channels formed with *KCNE2* were about 2-fold more sensitive to E-4031.[104] LY97241 was shown to inhibit K_v10.2 and K_v11.1 currents with K_i values of 1.5 μM and 2.2–19 nM, respectively.[111-113] K_v11.1 currents were also activated by mallotoxin, PD-118057, and ICA-105574 with K_d values of 0.5 μM, 3.1 μM, and 0.5 μM, respectively.[108,114,115]

Regulation

K_v11.1 currents were activated at voltages more positive than –50 mV and $V_{1/2}$ was – 15.1 mV,[116] whereas K_v10.2 currents were activated at around – 100 mV and $V_{1/2}$ was – 35.5 mV.[97] However, a 14–3-3 protein was associated with K_v11.1 in a phosphorylation-dependent manner at specific PKA sites and shifted $V_{1/2}$ in a hyperpolarizing direction by – 11.1 mV.[117] K_v11.1 may exist in a macromolecular signaling complex that includes 14–3-3 proteins and possibly AKAPs.[118] Importantly, the K_v11.1 protein can also assemble with *KCNE1* or *KCNE2* regulatory β-subunits.[103,104] Regarding inhibition, phorbol 12-myristate 13-acetate (PMA), an activator of protein kinase C (PKC), produced a potent dose-dependent block of K_v10.2 or K_v11.1 currents.[97,119] In addition, K_v11.1 currents were reduced by the cAMP-specific phosphodiesterase inhibitor Ro-20–1724 or the adenylate cyclase activator forskolin, which were shown to result in increased cAMP levels and PKA stimulation.[120]

KCNT1 (K_{Ca}4.1, Slo2.2, Slack) and *KCNT2* (K_{Ca}4.2, Slo2.1, Slick)

Tissue expression

KCNT1 (K_{Ca}4.1, Slo2.2, or Slack), which encodes for the Na^+-activated K^+ channel, was isolated from the brain cDNA library.[121] *KCNT1* and *KCNT2* (K_{Ca}4.2, Slo2.1, or Slick) are expressed in the heart, kidney and testis, as well as in the brain.[121-123] The functional expression of K_{Ca}4.1 has been demonstrated in the basolateral membrane of the thick ascending limbs of Henle's loop.[124] Pancreatic duct cells also expressed *KCNT1* and *KCNT2*.[13] Interestingly, the expression pattern of *KCNT1* and *KCNT2* was different between Capan-1 cells expressing functional CFTR channels and CFPAC-1 cells derived from a cystic fibrosis patient with a mutation in CFTR. Capan-1 cells express *KCNT1*, but not *KCNT2*, while CFPAC-1 cells express *KCNT2*,

but not *KCNT1*. This discrepancy indicates that the expression of *KCNT1* and *KCNT2* channels is in some way associated with the expression of functional CFTR. However, the function of these K^+ channels in pancreatic duct cells remains to be investigated.

Channel properties

$K_{Ca}4.1$ and $K_{Ca}4.2$ channels have large conductances of 180 pS and 140 pS in symmetrical 130 mM KCl.[122] In the basolateral membrane of the thick ascending limbs of Henle's loop, Na^+-activated K^+ channels had a conductance of 140–180 pS.[124] Regarding pharmacology, $K_{Ca}4.1$ was inhibited by bepridil and quinidine with K_i values of 1 μM and 90 μM, respectively.[125] $K_{Ca}4.1$ was activated by bithionol, niclosamide, loxapine, and niflumic acid with K_d values of 0.8 μM, 2.9 μM, 4.4 μM, and 2.7 mM, respectively.[125-127] $K_{Ca}4.2$ was inhibited by 1 mM quinidine and isoflurane,[122,128] and was activated by meclofenamic acid, flufenamic acid, and niflumic acid with K_d values of 80 μM, 1.1–1.4 mM, and 2.1 mM, respectively.[127,129]

Regulation

$K_{Ca}4.1$ was shown to be unusually inhibited by intracellular Ca^{2+} at 1 μM.[121] However, $K_{Ca}4.1$ may co-assemble with $K_{Ca}1.1$ subunits to generate Ca^{2+}-activated K^+ channels.[121] $K_{Ca}4.1$ and $K_{Ca}4.2$ channels were reported to be activated by intracellular Na^+ and K_d values of 41 mM and 89 mM in the presence of 30 mM internal Cl^-, respectively.[122] These channels were also activated by intracellular Cl^- or synergistically by Na^+ and Cl^-.[122,123] Intracellular ATP inhibited $K_{Ca}4.2$ directly, via the presence of a consensus ATP binding motif.[122] A similar ATP binding motif has not been demonstrated in the $K_{Ca}4.1$ sequences.[122,124] Interestingly, the PKC activator PMA increased $K_{Ca}4.1$ currents, but inhibited $K_{Ca}4.2$ currents.[130]

KCNK5 ($K_{2P}5.1$, TASK-2)

Tissue expression

Two-pore domain K^+ channels (K_{2P}) generate background K^+ currents over the whole membrane potential range.[131] The pH-sensitive K_{2P} subunits (TALK-1, TALK-2 and TASK-2) were shown to be expressed in pancreatic acini.[132] An electrophysiological study indicated that TASK-2 was expressed in HPAF, a human pancreatic ductal adenocarcinoma cell line.[10] *KCNK5* coding TASK-2 ($K_{2P}5.1$) was isolated from the brain cDNA library.[133] *KCNK5* is expressed in the kidney, liver, stomach, small intestine, colon, and pancreatic acinus.[132-134] The functional expression of $K_{2P}5.1$ has been demonstrated in kidney proximal convoluted tubule cells, which could be involved in volume regulation and HCO_3^- transport.[135] Clofilium-sensitive K^+ conductance, possibly $K_{2P}5.1$, was located in the luminal membrane of the monolayer of HPAF.[10] pH-sensitive K^+ channels on the luminal membrane of pancreatic duct cells may be physiologically relevant in terms of maintaining the electrical driving force for electrogenic HCO_3^- secretion and providing an exit pathway for K^+ secretion.

Channel properties

$K_{2P}5.1$ channels have an intermediate conductance of 50–78 pS.[133,136,137] Regarding pharmacology, $K_{2P}5.1$ was inhibited by quinine, clofilium, bupivacaine, and ropivacaine with K_i values of 22 μM, 25 μM, 26 μM, and 95 μM, respectively.[133,138,139] $K_{2P}5.1$ was activated by halothane, isoflurane, and chloroform, which are volatile anesthetics.[140]

Regulation

$K_{2P}5.1$ is very sensitive to extracellular pH in the physiological range, with a pK_a value of 7.5–8.3.[133,138,140,141] Phorbol 12,13-dibutyrate and PMA, activators of PKC, were shown to potentiate $K_{2P}5.1$ currents in *Xenopus* oocytes.[140] Extracellular ATP activated TASK-like channels ($K_{2P}3.1$ and/or $K_{2P}5.1$), possibly via the $P2Y_{11}$ receptor in thoracic aorta myocytes.[142] $P2Y_{11}$ receptors were reported to be expressed on the basolateral membrane of canine pancreatic duct epithelia, which increased cAMP and I_{sc}.[143] The $K_{2P}5.1$ channel is also osmosensitive and participates in cell volume regulation.[138] Therefore, pH-sensitive K^+ channels may be important on both the luminal (alkaline) and basolateral (acid) membranes of pancreatic ducts.

Potassium Channels in Pancreatic Cancer

Ion channels have been associated with the malignant phenotype of cancer cells, as well as contributing to virtually all basic cellular processes, including crucial roles in maintaining tissue homeostasis such as proliferation, differentiation, and apoptosis.[144] Several potassium channels have been suggested as the hallmarks of cancer,[145] including pancreatic duct adenocarcinoma.[144] For example, $K_{Ca}3.1$ channels have been correlated with the proliferation of pancreatic cancer.[49] In addition, the expression of G protein-activated inward rectifier potassium channel 1 ($K_{ir}3.1$) was markedly higher in pancreatic adenocarcinomas than in a normal pancreas, whereas $K_v1.3$ expression was decreased in pancreatic adenocarcinomas. Downregulation in the expression of $K_v1.3$ has been associated with metastatic tumors.[146] $K_v1.5$ was also shown to be highly expressed in pancreatic adenocarcinomas.[147] Furthermore, a specific monoclonal antibody that inhibits the function of $K_v10.1$ (EAG1) reduced tumor growth of BxPC3, a human pancreas adenocarcinoma cell line, which implicates this channel in cancer progression.[100] Altered pH homeostasis is known to be one of the key hallmarks of cancer.[148,149] Thus, pH-sensitive K_{2P} channels may also play a role in pancreatic adenocarcinoma. The human duct adenocarcinoma cell line, HPAF cells, were reported to express $K_{2P}5.1$ channels.[10] However, its contribution to cancer progression is still unknown. Although further studies on K^+ channels in pancreatic cancer must be performed, some candidates, such as $K_v10.1$, already have the potential to be diagnostic tools and therapeutic targets.[101]

Concluding Remarks

This review described the current status on the molecular basis for a number of K^+ channels found in pancreatic ducts. Electrophysiological studies on ducts and duct cells using microelectrode, patch-clamp, and Ussing chamber methods showed how some of these K^+ channels contribute to physiological processes in ductal secretion by providing the driving forces for anion transport and as partial accompanying partners in

secretion. Future studies are needed to verify the localization of K^+ channels to a polarized ductal epithelium and affirm their physiological function in secretion or associated cell processes such as cell volume regulation, as well as their participation in cell proliferation and apoptosis. The pancreas and especially the ductal epithelium are involved in a number of diseases including cystic fibrosis and pancreatitis.[150] Some target therapies should include K^+ channel openers to maintain or upregulate pancreatic secretion. Our knowledge regarding the role of K^+ channels in duct cell homeostasis remains relatively sparse. Because some K^+ channels are being regarded as the hallmark of cancer progression and emerging studies on pancreatic adenocarcinoma foreshadow similar trends, more knowledge is required in this area before specific K^+ channel openers or inhibitors can be used in the treatment of pancreatic diseases.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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